REMARKS

RCE

Amendment to claim 1 constitutes a submission for the Request for Continued Examination.

Claims

Claims 1–5, 17, 21, 22, and 33 are currently pending with claims 6–14, 19, 20, and 23–30 withdrawn from consideration due to election/restriction. Claims 15–16, 18, and 31–32 are cancelled without prejudice or disclaimer.

Claim Amendments

The claims have been amended to recite the polypeptides of the instant invention. Amended claim 1 incorporates the aspects of now-cancelled claims 31–32. Support for the amendment can be found throughout the specification as originally filed. See, for example, page 7, lines 16–19; the paragraph bridging pages 7 and 8; page 8, lines 10–14; and the disclosure contained in Figures 7, 8, and 9 of the instant specification.

Claim 22 is amended to recite a method claim and is supported by the paragraph bridging pages 14 and 15 of the instant specification.

Rejection under 35 U.S.C. §101 (utility)

Claims 1–5, 17, 21, 22, and 33 stand rejected under 35 U.S.C. § 101 as allegedly lacking an apparent or disclosed specific and substantial credible utility. Applicants respectfully traverse this rejection.

Applicants courteously submit that claims 1–5, 17, 21, 22, and 33 satisfy the utility requirements for the reasons set forth in the previous response in that, for example, the polynucleotides and polypeptides of the instant invention can be used as markers for epididymis tissue. This is clearly described in the specification. For instance, Figure 6 (human tissue sample) and Figure 7 (rat tissue sample) disclose that

the gene encoding ESRP polypeptides of the current invention is expressed in the male epididymis. Furthermore, Figure 9 discloses the tissue-specific in situ localization of HE6 polypeptides in the epididymis tissue of human and rat. Figure 10 describes the tissue specific expression of HE6 polypeptides in three different species of mammals. Also see, the "Brief Description of Figures" at pages 17–22 of the instant specification. Consequently, the polypeptides and/or polynucleotides of the instant invention can also be used as a unique and tissue-specific marker of epididymis tissue in mammals.

The art recognizes the association between human epididymis (HE) specific proteins in the male reproductive development. Thus, the activity of the compounds is associated with a real, specific and credible utility. In particular, there is an abundance of scientific literature outlining a role of human epididymis specific protein (ESRP) of the instant invention in spermatogenesis. For example, a search in PUBMED using the terms "human epididymis specific protein" AND spermatogenesis resulted in more than 50 such publications, out of which 13 were directed to human epididymis-specific proteins (HE1-6). See, attached Exhibit A. In these publications, it is disclosed that the heterotrimeric G-protein coupled receptor proteins (ESRP or HE6) play an important role in sperm maturation and in the overall process of spermatogenesis. See, the scientific publication by Kirchoff et al. (Andrologia, vol. 30, pages: 225-232, 1998) and the review article by the same author (Mol Cell Endocrinol., vol. 250, pages: 43-8, 2006). The murine and rodent homologs of HE6, ME6 and RE6, respectively have also been cloned and express a high degree of homology with the ESRP (HE6) polypeptides of the instant invention. Their tissue specific expression in the epididymis, along with their demonstrated role in the spermatogenesis process also imparts a scientifically credible, biological role of the claimed ESRP polypeptides in reproductive physiology. It is further submitted that Dr. Gottwald's declaration under 37 CFR § 1.132 (filed: 01/31/2002) provides additional corroborating scientific evidence that the polypeptides of the instant invention play an important role in male fertility. Although the Office Action at page 7 alleges that there are no such declarations of record with the instant application, it is respectfully submitted that the declaration was received by the USPTO on 09/24/2003 and is electronically accessible via the USPTO's Patent Application Information Retrieval (PAIR) system. The declaration (further copy attached) clearly demonstrates that the protein referred to as HE6 in the present application is a protein with biological significance. Using a knockout mouse model (i.e., mice lacking the

murine homolog of HE6), the studies demonstrate that both the cellular (for e.g., sperm count, sperm motility etc.) and the physiological (for e.g., male fertility rates) determinants of male reproductive capacity were compromised in the knockout animals. The declaration, together with the disclosure contained in the instant specification, provide a substantial, credible utility of the polypeptides of the instant invention in assessment of reproductive capacity or conversely, as a method for screening for substances that are suitable as male contraceptives. Also see Figure 2, and the accompanying legend and description of the figure at page 17 and page 24, respectively.

It is therefore submitted that tissue-specificity is sufficient to meet the utility statutory requirements of 35 U.S.C. § 101. Example 12 of the Revised Interim Utility Guidelines Training Materials relates to a marker that is specific for a cancer – which is a type of tissue specificity. There is no reason why tissue specificity for e.g., for epididymis tissue, would not analogously satisfy the utility requirements. Such a utility is specific, credible and substantial. Furthermore, Applicants respectfully submit that even though the guidelines do not require that tissue specificity be associated with a disease state, such is disclosed by the instant specification. The specification provides clear guidance as to the potential use of HE6 polypeptides for diagnosing initiation and/or progression of male infertility. Example 6 of the Synopsis of Application of Written Description Guidelines provides an example of a claim to a polypeptide that is useful because of its tissue specificity, as a marker for normal glial tissues, i.e., "glial specific G-coupled protein receptor". See, Pages 28–29 of the Guidelines. The presently claimed polynucleotides and polypeptides have the same type of utility, and therefore, are in conformance with the PTO requirements.

Applicants courteously submit that to maintain the rejection under these circumstances would not only be contrary to the Patent Office's own published standards, but also be blind to the overwhelming scientific evidence regarding the utility of the claimed polypeptides. Accordingly, it is respectfully submitted that the rejection should be withdrawn.

Rejection under 35 USC §112, first paragraph (written description)

The rejection of claims 1–5, 17, 21, 22, and 33 under 35 U.S.C. § 112, first

paragraph as allegedly lacking a written description is respectfully traversed.

The substance of claims 31 and 32 are now incorporated into claim 1 and claims 31-32 were not subject to this rejection. Thus, it is initially submitted that the rejection is, at least partially, rendered moot. However, the following further comments are provided. It is respectfully submitted that the specification coupled with a skilled worker's knowledge provides adequate guidance as to the structural and functional aspects of polypeptides of the instant invention. Guidance for the structural aspect of the claimed polypeptides is, for example, provided by the individual amino acid sequences, which are presented in the sequence listing section of the specification. Guidance for the functional aspect of the claimed polypeptide is provided by the disclosure of the peptides having GPCR signal transduction activity and the well-established recognition in the art of the biological activity of heterotrimeric G-protein coupled receptor family members. In short, the claims in the current form, with adequate support from the specification, fully comply with the statutory requirements under 35 U.S.C. § 112, first paragraph.

Furthermore, it is submitted that Applicant's disclosure regarding the utility of the claimed polypeptides as a biomarker of epididymis or contraceptive target for male fertility is fully commensurate with the relevant prior art. This area of biology has rapidly expanded since the discovery of the homologs of HE6 in rodents and mice, and the creation of knockout models. The specification teaches that the differential expression of the polypeptides of the instant invention in certain tissues confers their use as a biological marker for such tissues. It is courteously submitted that no evidence has been presented to refute the findings or the conclusions made in these publications. In addition, no evidence has been presented that any polypeptides of this invention, as differentially expressed in the epididymis, would not be effective as a tissue-specific marker or as a potential target for contraception. Thus, no reason to doubt applicants' disclosure of utility has been established.

Applicant has further reviewed the PTO's Written Description Guidelines and amended the claims in accordance with Example 9 beginning on Page 28 of the Synopsis of Application of Written Description Guidelines. The Federal Circuit in Enzo Biochem, Inc. v. Gen-Probe, Inc., 63 USPQ2d 1609 (Fed. Cir. 2002) has cited these Guidelines with approval. While applicants may not agree with the agency's interpretation of the elements necessary to meet the statutory requirements of 35

U.S.C. § 112, first paragraph, nonetheless, the pending claims have been amended to substantially conform to these.

The PTO's example provides a claim to sequences that hybridize to a recited sequence, and which encode proteins with a particular activity. ("An isolated nucleic acid that specifically hybridizes under highly stringent conditions to the complement of the sequence set forth in SEQ ID NO: 1, wherein said nucleic acid encodes a protein that binds to a dopamine receptor and stimulates adenylate cyclase activity.") The elements set forth as being adequate to fulfill the written description requirements included: (1) the protein's dopaminergic activity; (2) "a single species disclosed (a molecule consisting of SEQ ID NO: 1) that is within the scope of the claimed genus"; and (3) hybridization conditions that "yield structurally similar DNAs." The amended claims recite such elements, e.g., G-protein coupled receptor signal transduction activity, hybridization conditions (or equivalents thereof), and the immunogenicity of the claimed polypeptides. See amended claim 1.

Thus, it is evident that the specification clearly provides the information set forth by the U.S. Patent Office as needed to meet the statutory requirements for a hybridization claim.

In view of the above remarks, it is respectfully submitted that applicants' disclosure provides more than sufficient guidance to objectively enable one of ordinary skill in the art to make and use the claimed invention with an effort that is routine in the art. Withdrawal of the rejection under 35 U.S.C. §112, first paragraph, is respectfully requested.

Rejection Under 35 U.S.C. § 112, second paragraph

Claims 1–5, 17, 21, 22, and 33 stand rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite. Applicants respectfully traverse this rejection. Insofar as the claims no longer recite "derivates" of the claimed polypeptides, it is respectfully submitted that the rejections under 35 U.S.C. § 112, second paragraph are moot in view of the amendments. Withdrawal of the rejection is respectfully requested.

Rejection under 35 U.S.C. §102 (b) in view of Osterhoff et al.

Claims 1–5, 17, 21, 22, and 31–33 stand rejected under 35 U.S.C. § 102(b) as being allegedly anticipated by Osterhoff et al. (DNA and Cell Biol., vol. 16, pages: 379–389, 1997). Applicants respectfully traverse this rejection.

Osterhoff et al. is the Applicant's own publication, which was published April 1997, i.e., within a year prior to the filing of the parent application (Serial No.: 09/041,745). Applicants submit that the parent application provides an enabling disclosure of the presently claimed invention and provides an adequate written description of the presently claimed invention. Applicants further submit that the parent, like the instant application, meets the requirements of 35 U.S.C. §112, first paragraph, such that benefit of the parent application should be accorded, along with withdrawal of the rejection under 35 U.S.C. §102(b).

In view of the above and attached, it is respectfully submitted that the claims are in condition for allowance. However, should the Examiner have any questions or comments, he is cordially invited to telephone the undersigned at the number below.

The Commissioner is hereby authorized to charge any fees associated with this response to Deposit Account No. 13-3402.

Respectfully submitted,

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EXHIBIT A

PUBMED RESULTS OF THE SEARCH ON HUMAN EPIDIDYMIS PROTEINS (HE1-6) AND EPIDIDYMIS AND SPERMATOGENESIS

1: Gottwald U, Davies B, Fritsch M, Habenicht UF. Related Articles, Links

New approaches for male fertility control: HE6 as an example of a putative target.
Mol Cell Endocrinol. 2006 May 16;250(1-2):49-57. Epub 2006 Jan 24. Review.
PMID: 16442214 [PubMed - indexed for MEDLINE]

2: Kappler-Hanno K, Kirchhoff C. Related Articles, Links

Rodent epididymal cDNAs identified by sequence homology to human and canine counterparts.
Asian J Androl. 2003 Dec;5(4):277-86.
PMID: 14695977 [PubMed - indexed for MEDLINE]

3: Kamiya H, Sasaki S, Ikeuchi T, Umemoto Y, Tatsura H, Hayashi Y, Kaneko S, Kohri K. Related Articles, Links

Effect of simulated microgravity on testosterone and sperm motility in mice.
J Androl. 2003 Nov-Dec;24(6):885-90.
PMID: 14581515 [PubMed - indexed for MEDLINE]

4: Wang L, Ye W, Liu X, Guo Y. Related Articles, Links

[Combined use of steroid hormone and low dose gossypol for antifertility and its mechanism in rats]
Zhongguo Yi Xue Ke Xue Yuan Xue Bao. 2000 Jun;22(3):214-9. Chinese.
PMID: 12903462 [PubMed - indexed for MEDLINE]

5: Doiron K, Legare C, Saez F, Sullivan R. Related Articles, Links

Effect of vasectomy on gene expression in the epididymis of cynomolgus monkey.
Biol Reprod. 2003 Mar;68(3):781-8.
PMID: 12604626 [PubMed - indexed for MEDLINE]

6: Yeung CH, Perez-Sanchez F, Schroter S, Kirchhoff C, Cooper TG. Related Articles, Links

Changes of the major sperm maturation-associated epididymal protein HE5 (CD52) on human ejaculated spermatozoa during incubation.
Mol Hum Reprod. 2001 Jul;7(7):617-24.
PMID: 11420384 [PubMed - indexed for MEDLINE]

7: Deng X, He Y, Martin-Deleon PA. Related Articles, Links

Mouse Spam1 (PH-20): evidence for its expression in the epididymis and for a new category of spermatogenic-expressed genes.
J Androl. 2000 Nov-Dec;21(6):822-32.
PMID: 11105908 [PubMed - indexed for MEDLINE]

8: Okamura N, Kiuchi S, Tamba M, Kashima T, Hiramoto S, Baba T, Dacheux F, Dacheux JL, Sugita Y, Jin YZ. Related Articles, Links

A porcine homolog of the major secretory protein of human epididymis, HE1, specifically binds cholesterol.
Biochim Biophys Acta. 1999 Jun 10;1438(3):377-87.
PMID: 10366780 [PubMed - indexed for MEDLINE]

9: Kirchhoff C, Osterhoff C, Pera I, Schroter S. Related Articles, Links

Function of human epididymal proteins in sperm maturation.
Andrologia. 1998 Aug-Sep;30(4-5):225-32.
PMID: 9739419 [PubMed - indexed for MEDLINE]

Related Articles, Links

10: Hafez B, Goff L, Hafez S.

Recent advances in andrology research: physiopathology and clinical application to fertility and infertility.
Arch Androl. 1997 Nov-Dec;39(3):173-95. Review.
PMID: 9352030 [PubMed - indexed for MEDLINE]

Related Articles, Links

11: Itoh M, Hiramine C, Hojo K.

A new murine model of autoimmune orchitis induced by immunization with viable syngeneic testicular germ cells alone. I. Immunological and histological studies.
Clin Exp Immunol. 1991 Jan;83(1):137-42.
PMID: 1988220 [PubMed - indexed for MEDLINE]

Related Articles, Links

12: Prasad MR, Diczfalusy E.

New contraceptives for men. What are the prospects?
Int J Androl. 1983 Aug;6(4):305-9.
PMID: 6413430 [PubMed - indexed for MEDLINE]

Related Articles, Links

13: Hakami M, Mosavy SH.

Triorchidism with normal spermatogenesis: an unusual cause for failure of vasectomy.
Br J Surg. 1975 Aug;62(8):633.
PMID: 1174804 [PubMed - indexed for MEDLINE]